REMARKS

The Office Action dated January 31, 2011, has been carefully reviewed and the following comments are made in response thereto. In view of the amendments and the following remarks, Applicants respectfully request reconsideration and examination of this application and the timely allowance of the pending claims.

Written support for the claim amendments can be found throughout the specification and original claims. No new matter has been added.

Rejection under 35 U.S.C. 112, second paragraph

Claims 25, 26 and 28 were rejected as being indefinite as set forth on page 2 of the office action. The office action indicates that the claims never recite to what or where the substance is being administered. Applicants respectfully submit that amended claims 25, 26 and 28 recite administering an anti-human CXCR4 antibody or fragment thereof that inhibits SDF-1 binding to human CXCR4 to a human subject in need thereof. Accordingly, Applicant respectfully request the subject rejection be withdrawn.

The Rejection under 35 U.S.C. 112, first paragraph

Claims 25, 26 and 28 were rejected as failing to comply with the enablement requirement as set forth on pages 3-7 of the office action.

Applicants respectfully submit that no further experimentation is required to make and/or use the invention of amended claims 25, 26 and 28. It is important to be mindful that the question of enablement is one of predictability in view of what is known in the art. Consequently, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art (MPEP § 2164.03). The specification discloses that the structures of the chemokine receptor CXCR4 according to this invention were already known (see specification at pages 3-4). Additionally, the binding region of CXCR4 was also known at the time of filing as disclosed in Doranz (see appendix A) as being in the amino terminus and third extracellular loop of CXCR4 (see Doranz at Figure 1).

Furthermore, the specification discloses the physiological function of CXCR4 using mice lacking CXCR4. As mentioned on page 46, lines 3-6 of the present specification, high levels of CXCR4 transcripts were detected in the endothelium of developing blood vessel during embryogenesis. Histological examination of CXCR4 negative homozygous mutant embryos demonstrates that the large vascular branches were not presented in the mesenteries, whereas wild-type demonstrated that many large branches of superior mesenteric artery and vein supplying nutrient to the intestine were formed (see page

47, lines 2-8). Furthermore, Figure 8 indicates that CXCR4 negative homozygous mutant embryo vessels were singlular, whereas wild-type embryo vessels were paired between the artery and the vein. These experimental results demonstrate that CXCR4 is essential for the foundation of a mature vascular system which is supplied to the gastrointestinal tract by acting on the endothelial cells of blood vessels and regulating vascular branching and/or modeling.

It has been well known long before the filing of the present application that vascularization is essential to solid tumor growth and other diseases pathologically caused by neovascularization, inferring that preventing this process is a viable therapeutic approach. Applicants invention relies upon the novel finding that vascularization is suppressed in CXCR4 knockout mice, and that the CXCR4 antibodies which inhibit CXCR4 activation via ligand (i.e. SDF-1) binding can be employed in methods for treating solid tumors. These findings also serve to assist that CXCR4 antibodies disclosed in the present specification can be used as therapeutic agents for treating any disease pathologically caused by vascularization via suppressing vascularization.

In view of the foregoing, a person with ordinary skill in the art with the teaching of the specification and the common knowledge as of the filing date would be able to make and/or use the claimed method without undue experimentation.

Applicants note that the Examiner cites Stancovski, which was published 13 years before the filing date of the present application, to support the unpredicatable extrapolation of *in vitro* antibody function to *in vivo* effects. However, the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required (MPEP 2164.03). As discussed above, the specification adequately discloses to one skilled in the relevant art how to make and/or use the claimed invention without undue experimentation. Therefore, Applicants submit that the rejection is moot in view of the above remarks, withdrawal is requested.

Rejection under 35 U.S.C. 112, first paragraph

Claims 25, 26 and 28 were rejected as failing to comply with the written description requirement as set forth on pages 7-21 of the office action.

According to the Example 13 of the 2008 revised *Written Description Training Materials* (see http://www.uspto.gov/web/menu/written.pdf), a claim reciting "An isolated antibody capable of binding to antigen X" satisfies the written description requirement, even in a case where the specification provides no description of the structural, physical or chemical properties of any antibody falling within the scope of the claim. In other words, an antibody can be claimed without any disclosure of structure for the antibody.

Furthermore, as mentioned above, the specification clearly provides written description for anti-human CXCR4 antibodies that function (a) to inhibit the binding between the ligand human SDF-1 and human CXCR4 and (b) to treat a solid tumor, and/or a disease pathologically caused by vascularization, including neovascularization as set forth in the amended claims.

The Examiner relies on *In re Alonso* to rebut Applicant's arguments (see Office Action at page 17). *In re Alonso* is inapplicable in this instance and therefore cannot be relied upon to allege that the pending claims lack written description. The problem faced in *In re Alonso* was that the antigen was not specified in sufficient detail, i.e. it was undefined. If the antigen is specified in sufficient detail, such as in the specification and as was known in the art at the time of filing of the present application, it provides adequate written description for an antibody against the antigen (see *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2003)).

Alonso only discloses a hybridoma secreting monoclonal antibodies against a tumor from a single patient (*see In re Alonso*, p. 3). The specification of Alonso's application does not characterize the antigen to which the monoclonal antibodies must bind; it discloses only the molecular weight of the antigen (a 221 kDa tumor surface antigen) in an Example (*see In re Alonso,* pp. 3, 9). Furthermore, the antibody was described in terms of being idiotypic to the neurofibrosarcoma of said human (*see In re Alonso*, p. 9). In other words, *In re Alonso* dealt with an undefined antigen. Alonso's claim to a broad genus of antibodies was held to lack sufficient written description because the application only disclosed an undefined antigen.

In contrast, in the instant application, the antigen is specified (i.e. human CXCR4). The specification clearly discloses the antigen including the amino acid sequence (see SEQ ID NO: 1 (human CXCR4); SEQ ID NO: 5, 9 (human SDF-1)). Contrary to the allegations in the Office Action implying that at the time of the invention 12G5 was the only known antibody against CXCR4, at the time of the invention, numerous antibodies against (1) CXCR-4 and (2) SDF-1 were known, some of which were even commercially available. At the time of the invention, it was also well-known that antibodies can readily be made against a known antigen. Accordingly, the claims have adequate written description and therefore the rejection should be withdrawn.

As the Examiner is aware and as previously noted by the Applicants, as long as an applicant has a *fully characterized* antigen by its structure, formula, chemical name, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen. As previously noted by the Examiner, the specification discloses the amino acid and nucleotides sequences of human CXCR4 (SEQ ID NO: 1 and page 14, lines 24 to 26) and human SDF-1 (SED ID NO: 5, 9 and page 15, lines 1 to 20).

Applicants again note, as set forth in the previous response, that the specification discloses: (i) that both SDF-1 and CXCR4 are necessary for neovascularization (page 2, line 20 to page 4, line 10), (ii) known structural of details of CXCR4 (page 2, line 20 to page 4, line 10), (iii) the role of SDF-1 (page 2, line 20 to page 4, line 10), (iv) anti-SDF-1 antibodies (page 17, lines 13 to 20) and anti-CXCR4 antibodies (page 18, lines 10 to 11), (v) how to make anti-SDF-1 and anti-CXCR4 antibodies (page 26, line 25 to page 32, line 36); and (vi) methods of treating cancer, treating a pathology caused by neovascularization, and suppressing vascularization with such antibodies (see page 38, lines 15 to 25). Accordingly, each element of the claims is disclosed in the specification and one of skill in the art would recognize what is claimed in sufficient detail to reasonably conclude that the inventors were in possession of the claimed invention (see MPEP 2163).

The arguments raised in the Office Action do not change the fact that the pending claims clearly comply with the written description requirement. The specification adequately describes anti-SDF-1 and anti-CXCR4 antibodies used in the methods and adequately describes the methods such that the skilled artisan would have considered Applicants in possession of the claimed invention.

As described above, at the time of the invention, those of skill in the art would have known how to make antibodies against a known antigen (such as *e.g.* CXCR4). If a receptor and its ligand are known, one of skill in the art can select an antibody having neutralizing activity well-known methods, such as e.g. by detecting the binding between the receptor and its ligand, without undue experimentation. Furthermore, at the time of invention, it was known that is possible to obtain neutralizing antibodies against CXCR4 and SDF-1.

The specification also adequately describes the claimed methods of the invention such that a skilled artisan would have considered the Applicants to be in possession of the claimed invention. In particular, the specification discloses the claimed methods and diseases (see page 38, lines 14 to 36 of the specification) and includes experimental evidence demonstrating Applicants' possession of the claimed invention (see page 48, lines 4 to 8; page 50, lines 14 to 29; page 52, line 19 to page 60, line 10 of the specification).

Thus, given the disclosure of the specification, those of skill in the art would clearly recognize that the inventors were in possession of the claimed invention and that therefore the claims comply with the written description requirements. Accordingly, Applicants request withdrawal of the lack of written description rejection.

Conclusion

It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicants respectfully request a telephonic

or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

Respectfully submitted,
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